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How reliable is ictal duration to differentiate psychogenic nonepileptic seizures from epileptic seizures?

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ABSTRACT

We sought to investigate (1) differences in ictal duration between psychogenic nonepileptic seizures (PNES) and epileptic seizures (ES), (2) the odds of being PNES when seizures last ≥5 min, and (3) the value of ictal duration as a diagnostic test to differentiate PNES from ES. We retrospectively reviewed video-EEG recordings and tabulated ictal durations of all PNES and ES. We estimated the mean ictal durations of PNES and ES using linear mixed models. The odds of being PNES when seizures last ≥5 min were estimated using logistic regression. We used receiver operating characteristics (ROC) curves to study the overall diagnostic accuracy of ictal duration in differentiating PNES from ES. We studied 441 ES and 341 PNES recorded from 138 patients. The mean ictal duration of PNES (148.7 s, 95% CI: 115.2–191.8) was significantly longer ($p < 0.001$) than that of ES (47.7 s, 95% CI: 37.6–60.6). The odds of being PNES was about 24 times higher (Odds ratio: 23.8, 95% CI: 7.9–71.3) when the ictal duration was ≥5 min. The ROC curve yielded an area under the curve of 0.80 (95% CI 0.73–0.88). Youden's index identified 123.5 s as the optimal threshold to diagnose PNES with 65% sensitivity and 93% specificity. Our results indicate that ictal duration is a useful test to raise suspicion of PNES. When a seizure lasts ≥5 min, it is 24 times more likely to be PNES with the potential risk of misdiagnosis as status epilepticus.

1. Introduction

Differentiating psychogenic nonepileptic seizures (PNES) from epileptic seizures (ES) is a major diagnostic challenge faced by clinicians and the rate of misdiagnosis is as high as 20–30% [1,2]. The misdiagnosis of PNES as ES often leads to unnecessary interventions and treatment with antiepileptic drugs resulting in adverse outcomes including death [3,4]. Prolonged PNES mimicking status epilepticus ("pseudostatus epilepticus") is in particular a challenging condition to diagnose [5].

The gold standard diagnostic test for seizures is video-electroencephalographic (VEEG) monitoring. However, it is an expensive investigation with limited availability. Therefore, researchers have evaluated the use of semiology without EEG in differentiating PNES from ES. The results indicate variable diagnostic accuracy depending on the experience of the observer [6,7].

One major drawback in using most semiological features is the lack of quantifiable objective measurements. Being an objective measure, ictal (seizure) duration is a unique semiological sign. Several studies have found that ictal duration is significantly longer in PNES compared with ES (Table 1) [8–14]. However, only one study presents diagnostic accuracy at a single threshold [15], and none of the studies, as summarized in Table 1, provides information on the overall diagnostic accuracy of the ictal duration as a test. Seizures lasting ≥5 min are diagnosed as status epilepticus and treated aggressively. Hence, there is a potential risk for PNES to be misdiagnosed as status epilepticus because PNES tend to last longer than ES.

Against this backdrop, we sought to investigate three research questions in relation to ictal duration;

(1) How does ictal duration of PNES differ from that of ES?
(2) When seizures last ≥5 min, what are the odds of them being PNES, which can potentially be misdiagnosed as status epilepticus?
(3) How reliable is ictal duration as a diagnostic test to differentiate PNES from ES?

We hypothesized that ictal duration is a reliable test to differentiate PNES from ES, and when a seizure lasts ≥5 min the odds are higher for being PNES with the potential risk of misdiagnosis as status epilepticus.

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Table 1
Summary of previous studies on the diagnostic value of ictal duration to differentiate ES from PNES.

Reference	Mean age (SD)		N subjects (N seizures)		Seizure duration mean in seconds (SD)		Seizure duration median in seconds		Conclusions
	ES	PNES	ES	PNES	ES	PNES	ES	PNES	
Azar (2008)	28.5 (9.9)	36.2 (13.3)	GTCS 15 (23) FLHS 9 (21)	16 (24)	65 (24) 43 (19)	140 (62)	NS	NS	PNES longer than ES ($p = 0.003$)
Brown (1991)	37.1 (12.3)	33.2 (8.2)	25 (NS)	23 (NS)	40.2 (17.8)	2547.3 (4096.2)	NS	NS	PNES longer than ES ($p = 0.004$)
Henry (1998)	NS	NS	133 (70)	24 (28)	NS (all seizures <2 m)	438	NS	NS	ES < 2 m, PNES ≥ 2 m ($p < 0.001$)
Jedrzejczak (1999)	25	25	55 (74)	55 (221)	119 (50)	1427 (4035)	NS	NS	PNES longer than ES ($p < 0.001$)
Kanner (1990)	NS	NS	12 (63)	44 (111)	28.2 (7.79)	173.1 (158)	26.6	132.3	PNES longer than ES ($p = 0.01$)
Pierelli (1989)	Total cohort-35.2 (12.8)		12 (208)	15 (87)	83.3 (50.5)	724.5 (1557.5)	60	240	PNES longer than ES ($p < 0.0001$)
Saygi (1992)	26.4 (14)	38.2 (12)	11 (63)	12 (29)	51 (30)	176 (166)	NS	NS	PNES longer than ES ($p < 0.05$)
Syed (2011)	Median 39	Median 36	23 (84)	12 (36)	NS	NS	NS	NS	Seizure >2 min diagnoses PNES with sensitivity 67% & specificity 48%

ES = epileptic seizure; PNES = psychogenic nonepileptic seizure; N = total number; NS = not specified; SD = standard deviation; GTCS = generalized tonic-clonic seizure; FLHS = frontal lobe hypermotor seizure.

2. Methods

We retrospectively reviewed all consecutive VEEG recordings of patients who underwent monitoring at the epilepsy monitoring unit (EMU) of Monash Medical Centre, Melbourne, Australia from May 2005 to June 2015. We only included adults (≥18 years) and selected studies which captured PNES and ES in isolation or combination. Events with subjective symptoms without obvious semiological features were excluded. Similarly, electrographic epileptic seizures without clinical semiology were excluded from the analysis.

The VEEG data were acquired using the Compumedics digital EEG system (Compumedics Ltd., Melbourne, Australia) with the international 10–20 system of electrode placement. Antiepileptic drug (AED) tapering and sleep deprivation were routine practices in the EMU. We did not use other seizure provocation techniques such as hyperventilation, intermittent photic stimulation, and placebo injections.

We collated clinical and demographic data from medical records. We reviewed all seizures captured on VEEG during the study period. The final diagnosis of PNES or ES was based on the consensus opinion of at least two epileptologists after reviewing clinical information, investigation results, and VEEG findings, including semiology. The diagnosis had been established following the VEEG monitoring, in the multidisciplinary meeting, prior to the current study. We considered this consensus diagnosis as the "gold standard" for our study. The reader is referred to Seneviratne et al. for a more detailed account [16]. For the current study, two investigators, an epileptologist (US) and an EEG technologist (EM), studied each seizure video carefully, in synchrony with the EEG, to measure the ictal duration. We measured ictal duration from the onset of first observable behavioral change to the offset of clinical semiology, based on the consensus between the two raters. Psychogenic nonepileptic seizures were classified based on the semiology as described previously [16].

We estimated the mean ictal duration using linear mixed models adjusting for repeat measures. As the ictal duration had a positively skewed distribution, logarithmic transformation was applied prior to the analysis with the results reported as geometric means and 95% confidence intervals (CI). The risk of being PNES when a seizure lasts 5 min or more was estimated using logistic regression adjusting for repeat measures with the results reported as an odds ratio and the corresponding 95% CI.

We performed receiver operating characteristic (ROC) curve analysis to study the overall diagnostic accuracy of ictal duration for diagnosing PNES. The receiver operating characteristic curve of ictal duration was constructed by plotting sensitivity against 1-specificity at a range of thresholds [17]. We used the area under the curve (AUC) as the measure of overall diagnostic accuracy [18]. The AUC was interpreted as follows; 0.5, differentiation of PNES from ES no better than chance; 0.6–0.69, poor differentiation; 0.7–0.79 fair differentiation; 0.8–0.89, good differentiation; and 0.9–1, outstanding differentiation [18]. When a patient had more than one seizure recorded, we used the mean ictal duration of the subject as our measure to construct the ROC curve. When both ES and PNES were captured from the same subject, we calculated means separately for the two types of events. The optimal cut-off point for the ictal duration to differentiate PNES from ES was determined using Youden's index [19].

The data analyses were performed with IBM SPSS (version 21) statistical software package (IBM Corporation, New York, USA) and SAS software version 9.4 (SAS Institute, Cary, NC, USA). A p value <0.05 indicated statistical significance.

The study protocol was approved by the Human Research Ethics Committees of Monash Health.

3. Results

We studied a total of 782 seizures (ES,441; PNES,341) from 138 patients consisting of 72 (52.2%) females and 66 (47.8%) males with the mean age (±SD) of 43 ± 16.6 years (range, 18–91). A higher proportion of females was seen in the PNES group compared with the ES group (71% vs 37%). Mean ages of ES and PNES cohorts were comparable (44.2 ± 17.8 & 41.7 ± 15.3 respectively). Epileptic seizures alone were captured from 73 (52.9%) patients, whereas 62 (44.9%) had only PNES. Both ES and PNES were recorded from three patients (2.2%). In the "ES alone" group, 62 (84.9%) and 11 (15.1%) had focal and generalized epilepsy syndromes, respectively. Different ES types in the cohort are summarized in Table 2. Table 3 highlights semiologic subtypes of PNES and their corresponding durations. The mean duration of VEEG monitoring was 4.5 ± 1.5 days.

In the cohort, 93% of ES lasted <2 min compared with 48% in PNES. Furthermore, 21.4% of PNES were 5 min or longer compared with 1.1% in ES (Table 4 & Fig. 1 A). In the mixed model analysis, the geometric means of the ictal duration of ES and PNES were 47.7 (95% CI: 37.6–60.6) and 148.7 (95% CI: 115.2–191.8) seconds, respectively. PNES was about three times longer than ES and the difference was statistically significant ($p < 0.001$).

The analysis further revealed that the odds of being PNES were about 24 times greater (odds ratio: 23.8, 95% CI: 7.9–71.3) when the ictal duration was 5 min or more compared to those with <5 min of ictal duration.

The ROC curve revealed an AUC of 0.80 (95% CI 0.73–0.88) indicating a good overall diagnostic accuracy of the test (Fig. 1B). Table 5 summarizes sensitivities, specificities, and predictive values at different cut-off values of ictal duration for PNES diagnosis. The diagnostic specificity for PNES increases and the sensitivity decreases with increasing ictal